Februari 2004

Acetylcysteine and diarrhoea

Introduction

Acetylcystein (Mucomyst®) was approved for marketing in the Netherlands in December 1964, initially for infusion only. In 1977 acetylcystein (Fluimicil®) was approved for oral use. Acetylcystein has been approved for the following indication: *pulmonary diseases, which require reduction the production of viscous mucus in order to facilitate coughing up sputum, for example bronchitis, asthma, COPD, mucoviscidosis and bronchiectasis* [1]. In 1985 acetylcystein was approved *for the treatment of paracetamol (acetaminophen) poisoning* [1]. The most frequent adverse events with acetylcystein as mucolytic agent include gastrointestinal complaints, such as nausea and vomiting. In patients with (a history of) peptic ulcers, acetylcystein may irritate gastric mucosa [1]. Allergic reactions may occur rarely. Intravenous Acetylcystein used in treating paracetamol (acetaminophen) poisoning may cause vasodilatation, flushing and allergic reactions such as rash, pruritus, nausea, dizziness or bronchospasm [1]. Until October 2002, the Netherlands Pharmacovigilance Centre Lareb received 63 reports of gastrointestinal complaints related to the use of acetylcystein. Twelve reports concerned diarrhoea. Diarrhoea has not been mentioned in the Summary of Product Characteristics (SPC) of acetylcystein [1].

Reports

An overview of the reports received by the Netherlands Pharmacovigilance Centre is provided in Table 1.
Five of the twelve adverse events have been reported by a general practitioners. Four adverse events have been reported by pharmacists, and three by a specialist doctor. The time to onset varies from a couple of hours after starting to 5 months after starting, but in most cases (8) diarrhoea occurred within a week after starting with acetylcystein. One patient used amoxicillin as concomitant medication, which is strongly associated with diarrhoea. Four of twelve patients suffered from other gastrointestinal complaints, such as vomiting and abdominal pain. In two of the patients the diarrhoea decreased after dosage reduction.

Other sources of information

Literature

Ferrari reports of safety data and interactions in relation to the use of acetylcystein. Clinical studies with 784 subjects treated orally and 410 treated parentally showed that gastrointestinal side-effects are the most common reported adverse effects of the use of acetylcystein. The gastrointestinal complaints include pyrosis, nausea, dyspepsia, diarrhoea and rarely vomiting. However, these adverse effects were not more frequently reported with acetylcystein compared with placebo. Additional data from spontaneous reports from five European countries also revealed that gastrointestinal complaints are the most common reported adverse effect [2]. Miller et al. report safety data obtained from acetylcystein treated patients with paracetamol (aminoacetophen) overdose. Vomiting and diarrhoea were the most common reported gastrointestinal adverse events. Acetylcystein appeared to be the main important cause of diarrhoea. The incidence of diarrhoea increased with the number of doses and was observed in 43.5% of the patients treated with 15 or more doses (140 mg/kg loading dose and 17 maintenance doses of 70 mg/kg per dose given at 4 hr intervals over a 3-day period) [3]. A Swiss Post-Marketing Surveillance study of the oral use of acetylcystein by patients suffering from non-obstructive chronic bronchitis showed that gastrointestinal side effects occurred in 15 of 407 patients (3.7%). One patient suffered from diarrhoea (0.2%) [4].

Table 1. Reports of diarrhoea associated with the use of Acetylcystein

Sex, age	Dosage	Concomitant Medication	Suspected ADR	Time to onset, Outcome	Remarks

M, 38	200mg 3dd	unknown	diarrhoea	2 days, unknown (drug withdrawn)	
M, 30	200mg 3dd	unknown	diarrhoea	1 hour, unknown	
F, 58	600mg 1dd	amoxicilline	diarrhoea, vomiting	unknown unknown (drug withdrawn)	diarrhoea is a known adverse effect of amoxicillin
F, 44	200mg 3dd	unknown	diarrhoea, vomiting	4 hours, unknown (drug withdrawn)	
M, 80	600mg 1dd	ipratropiumbromid, prednisolone, salbutamol, terfenadine, bisoprolol	abdominal pain, diarrhoea	2 hours, unknown	unknown whether patient suffers from rheumatoid arthritis or ulcerative colitis (crohn). but suspected time-relationship
M, 51	200mg 3dd	prednisolone, sulfasalazine, terbutaline	diarrhoea	2 days, unknown	
F, 72	200mg 3dd	flurazepam	abdominal pain diarrhoea	1 day, unknown	
M, 59	200mg 2dd	salbutamol, beclomethasone	diarrhoea	unknown, recovered	
F, 73	200mg 3dd	methformin, diltiazem, isosorbidedinitrate, glibenclamide acenocoumarol,	diarrhoea	5 months, diarrhoea decreased	diarrhoea decreased after dosage reduction.
F, 62	600mg 3dd	tamoxifen, atenolol, levothyroxine ipratropiumbromid, nitrazepam	diarrhoea	4.5 months, unknown	
F, 4	200mg 2dd	none	diarrhoea	within 1 week, recovered after dosage reduction	
F, 3	200mg 2dd	none	diarrhoea	within 1 week after discontinuation, recovered	

Databases

The database of the WHO Monitoring Centre contains 140 cases of diarrhoea in association with the use of acetylcystein (ROR 2.22; 95% CI 1.87-2.64).

Mechanism

Acetylcystein acts as a mucolytic agent by reducing the viscosity of the bronchial mucus. Acetylcystein possesses a free sulfhydryl group that can break disulphide chemical bonds [1]. The mechanism for diarrhoea, however, is not known. Diarrhoea after intravenous use of acetylcystein may suggest a systemic mechanism. However the short time to onset after oral use of acetylcystein contradicts this theory.

Conclusion

Twelve cases in the database of the Netherlands Pharmacovigilance Centre Lareb show a possible relation of diarrhoea and acetylcystein. In two of the cases the diarrhoea has been dose-dependent. The findings are supported by data from the database of WHO and literature.

References

1. Dutch summary of product characteristics of acetylcysteïne, www.cbg-meb.nl (assessed July 2002). 2002.
2. Ferrari V. Safety and Drug interactions of oral acetylcystein related to utilization data. European Journal Dis61, Suppl. 111, 151-157. 1980.
3. Miller LF and Rumack BH. Clinical Safety of High oral doses of acetylcysteine. Seminars in Oncology10 no.1 Supplement 1, 76-85. 1983.
4. Mautone G and Lualdi P. Mittelfristige Behandlung der chronischen bronchitis mit N-acetylcystein. Therapiewoche Schweiz6,8, 649-652. 1990.